REMARKS

The foregoing amendments and the following remarks are submitted for entry and consideration in response to the communication dated December 24, 2009.

Status of the Claims

Claims 37-51 are pending and examined in the application. Claims 37, 41, 42, 43, 44, 45 and 51 have been amended and new claims 52 and 53 are presented in order to more particularly point out and distinctly claim that which Applicants regard as the invention. With respect to all amendments and canceled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and, moreover, has not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications. No new matter is added by the amendment of the claims or in the newly presented claims.

Support for the amended claims and new claims can be found generally through Applicants' specification. Applicants direct the Examiner to the specification generally, including the claims as filed and as previously pending. Particular support for the amendment to claims 42 and 43 may be found in the specification including at least at page 11 lines 28-30. New claim 52 is supported throughout the specification, including at least in original claim 10, at page 16 lines 17-19, Figure 33, page 32 lines 20-24, page 161 lines 9-13, and Table 6. New claim 53 is supported throughout the specification, including at least in original claim 15 and at page 12 lines 9-15, page 16 lines 17-19, page 19 lines 1-2 and lines 10-11, Figure 33, page 32 lines 20-24, page 161 lines 10-13, and Table 6.

Claim Rejections - 35 U.S.C. 112, First Paragraph

Enablement

Claims 37-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, the Examiner maintaining this rejection against new claims 37-51. The Examiner remarks that the claims encompass the exact same cells that were previously

claimed and alleges that "although not explicitly recited in the claims that the cells are 'embryonic-like', the specification defines the pluripotent animal stem cells as pluripotent embryonic-like stem cells". The Examiner additionally reiterates that "the characterization Applicant's cells are pluripotent is not predictable, as stated previously, and additionally, because the cells express markers that fail to uniquely identify pluripotent stem cells, such as embryonic stem cells, because these markers as expressed in other cell types". The Examiner additionally remarks that "although specification has shown that the claimed cells express alkaline phosphatase and SSEA-4, this does not provide sufficient guidance to show that these cells are pluripotent". The Examiner then further states that "Applicants cells would not be considered pluripotent, because they express markers and have phenotypes and characteristics that fail to establish that they are pluripotent". In concluding, the Examiner remarks that, "in view of the lack of teachings or guidance provided by the specification, with regard to the identification and characterization of the claimed cells, the state of the art, which clearly shows that particular markers fails to establish or uniquely identify ES cells, it would have required undue experimentation for one of ordinary skill in the art to make and use the claimed cells".

Applicants respectfully disagree, traverse this rejection, and submit that rejected claims 37-51 are fully enabled. Applicants again assert that the instantly claimed isolated postnatal stem cells are new, novel, and unique from any stem cells in the prior art and have their own distinct and specific features and character. Claims 37-51 are particularly directed to isolated postnatal animal stem cells capable of self-renewal and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages. These cells are derived from postnatal animal cells or tissues.

The Examiner has set out rejections and arguments which relate to language and characteristics which are not recited in the presently pending and rejected claims. The claims do not recite that the claimed cells are pluripotent, and certainly are not intended to be or should be interpreted to cover embryonic stem cells. Applicants do not understand or agree with the Examiner's focus as to whether the cells are pluripotent, as she defines that, or that they express markers and have characteristics that fail to establish that they are pluripotent. The novel

claimed cells of the instant invention are unique and do not correspond to cells previously described. They have their own unique characteristics. In fact, the cells have certain characteristics previously ascribed to pluripotent cells and other characteristics previously ascribed to embryonic cells. Therefore, they are not precisely like any pluripotent or embryonic cells which have been prior isolated, described, anticipated or even suggested. The claimed cells are characterized as isolated postnatal cells having particular characteristics and capabilities. The Examiner should and must interpret the claims based on the recited language and not on alleged characters or comparisons which are not present in the claim language and not relevant to the pending claims. In stating that the "claims encompass the exact same cells that were previously claimed", the Examiner clearly has not fully considered the language of the new claims.

Based on a reading of the specification, including the teaching of the isolation and the characterization and capabilities of the claimed postnatal animal stem cells, capable of self-renewal and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages, one skilled in the art is enabled to make and or use the claimed cells. The cells are derived from postnatal animal cells or tissues, thereby having the benefit of a straightforward and readily available source for isolation, and have characteristics thereby of postnatal cells, while having unique differentiative capacity previously only attributed to cells from an embryo or fetus, such as embryonic stem cells or embryonic germ cells. The cells are quite unique and one skilled in the art could readily isolate, identify, and use the postnatal stem cells, including from any animal species. The specification describes methods of isolating the cells, suitable exemplary markers and assays for characterizing the cells, including cell surface markers and differentiation assays and assessments, and characterizes the claimed postnatal animal cells from various animal species, including from rats, rabbits, mice, humans and avians. The methods for isolation and characterization are readily practiced by one of skill in the art and could be completed on these or any animal species, using a postnatal animal cell or tissue source without undue experimentation. The isolation and characterization of cells uses standard methods and capabilities of the skilled artisan and this, coupled with the unique differentiative capacity of the

claimed cells, which can be readily assessed and evaluated using known and described techniques, markers and assays, enables the skilled artisan to isolate and use the claimed postnatal stem cells. The artisan will recognize the postnatal stem cells by their derivation and in their unique differentiative capacity.

Applicants submit that claims 37-51, including as above amended, as well as now presented new claims 52 and 53, comply with the 35 U.S.C. 112, first paragraph, enablement requirement.

In view of the foregoing remarks and amendments, Applicants submit that the Examiner's enablement rejection under 35 U.S.C. 112, first paragraph, may properly be withdrawn.

Written Description

The Examiner rejects claims 37-51 as failing to comply with the written description requirement, alleging that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The Examiner remarks that the "claims encompass the exact same cells that were previously claimed", therefore the written description issues that were addressed regarding the claimed cells continue to apply to the newly amended claims. The Examiner asserts that the specification fails to describe the markers and specific characterization of the cells, and the skilled artisan, although recognizing that specific markers and characteristics identify pluripotent cells, could not envision which of such markers or characteristics would uniquely identify Applicamts' claimed cells. The Examiner particularly states "Specifically, the specification fails to describe the markers and specific characterization of the cells (such as teratoma formation), and the skilled artisan, although recognizing that specific markers and characteristics identify pluripotent cells, could not envision which or such markers or characteristics, would uniquely identify Applicants' claimed cells".

Applicants respectfully disagree and traverse this rejection. Applicants argue that the rejected claims 37-51 provide identification and characterization of the claimed cells to establish and uniquely identify the instant stem cells for the skilled artisan. Applicants particularly point out that new claims 52 and 53 provide specific characteristics and markers that identify the postnatal stem cells and meet the written description requirement. The specification describes and teaches the isolation, characterization and capabilities of the claimed postnatal animal stem cells capable of self-renewal and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages. The specification describes isolating and characterizing the postnatal stem cells and describes various exemplary markers to confirm the identity, and also the capacity, of the cells.

Applicants submit that the source of the cells and their capability to differentiate to cells of endodermal, ectodermal and mesodermal lineages provides sufficient and suitable distinguishing characteristics. Additionally, the specification and claims provide supplemental markers for complementary assessment, which characterize the postnatal stem cells and further establish their unique nature versus any other previously described, isolated or recognized postnatal or embryonic cell(s). Applicants underscore to the Examiner that these markers are detailed as exemplary characters and that in the Tables 7-10, in each instance as noted at the bottom legend of the Table "A blank space indicates that cells were not tested". The Examiner has wrongly interpreted a blank as indicating no expression of the noted marker(s) by the requisite cells being tested, which is wholly incorrect and has been utilized in her arguments to allege that any markers do not provide a positive identifying characteristic for the cells. In fact, the cells were not tested for that particular marker when a blank space is present. Applicants argue, in contrast, that the skilled artisan may utilize this specification teaching to assist then in working with and characterizing the isolated postnatal stem cells.

Applicants assert that claims 37-51, including as above amended, and new and now presented claims 52 and 53 comply with the written description requirement and contain subject matter which was described in the specification in such a way as to reasonably convey to one

skilled in the art that the inventor(s) had possession of the invention at the time the application was filed.

In view of the foregoing remarks and the above amendments, Applicants submit that the Examiner's 112, first paragraph, rejection regarding new matter is obviated and should be withdrawn.

Claim Rejections – 35 USC § 112, Second Paragraph

Claims 41-43 are rejected under 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The Examiner alleges that there is no antecedent basis for the recited limitation "The stem cells of claim 37" in claims 41-43, because claim 37 relates to a single, not a plurality, of stem cells. Claims 41-43 have above been amended to address this rejection. In particular, claim 41 now refers to the "stem cell", and claims 42 and 43 have been amended to recite "Isolated stem cells consisting of a population of the cell of claim 37". In each of the amended claims there is clear and definite antecedent basis for the recitations in the claims. Applicants respectfully submit that the language of claims 41-43, including as above amended, is clear and definite in each claim and request that the claim rejections under 35 U.S.C. §112, second paragraph, be withdrawn.

The §102 Rejections

Rejection over Capecchi et al

Claims 37, 38, 40-43, 45, 48, 49 and 51 are rejected under 35 USC 102(b) as being anticipated by Capecchi et al [Scientific American 270(3): 34-41 (1994)]. Capecchi teaches the inactivation of target genes by homologous recombination and the insertion of a *neo* resistance gene, which serves as a positive selection marker, in mouse ES cells. The Examiner alleges that the claimed cells are not distinguished from those taught by Capecchi, arguing that the Capecchi cells fulfill the limitations of the claims (the differentiation to cells of any endodermal,

ectodermal, mesodermal lineage) by showing the generation of mice and that Capecchi also anticipates the methods of producing genetically engineered cells because it teaches "transfection of pluripotent embryonic-like stem cells". The Examiner notes that the limitation in the claims that the cells are isolated from a postnatal source fails to distinguish the claimed cells from the cells of the art.

Applicants disagree and respectfully traverse this rejection. To anticipate a claim, a prior art reference must teach or suggest each and every element and limitation of the claim. Claims 37, 38, 40-43, 45, 48, 49 and 51, including as above amended, are not taught by Capecchi et al. Capecchi teaches genetically engineered mouse ES cells, which are embryonic stem cells derived from a mouse embryo and having embryonic nature and character. In sharp and significant contrast, the instant claimed cells are isolated postnatal animal stem cells, capable of self-renewal and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages, genetically engineered to express a gene or protein of interest. The claimed cells are derived from postnatal animal cells or tissues, in other words, after birth. The instantly described and claimed cells are not derived from embryonic cells or tissue.

Capecchi describes targeted gene replacement in mice which requires the germ line transmission of the target via ES cells. The Capecchi method as described requires an embryonic cell capable of germline transmission. This could not be accomplished as described with a postnatal cell. The instantly described and claimed cells are postnatal cells and are not derived from embryonic tissue. Applicants submit that there exists a well recognized dogma of difference between an embryonic cell or tissue and a postnatal cell or tissue. The specification describes the usefulness of embryonic cells and their significant limitations including at page 4 lines 10-21 as follows:

> *ES cells are used for both in vitro and in vivo studies. ES cells retain their capacity for multilineage differentiation during genetic manipulation and clonal expansion. The uncommitted cells provide a model system from which to study cellular differentiation and development and provide a powerful tool for genome manipulation, e.g. when used as vectors to carry specific mutations into the genome (particularly the mouse genome) by homologous recombination (Brown et al., 1992). While ES cells are a potential source of cells for transplantation studies, these prospects have been frustrated by the disorganized and heterogeneous nature of development in culture, stimulating the*

necessary development of strategies for selection of lineage-restricted precursors from differentiating populations (Li et al., 1998). E cells implanted into animals or presented subcutaneously form teratomas-tumors containing various types of tissues containing derivatives of all three germ layers (Thomson et al., 1988).

While ES cells, as above noted, are recognized as spontaneously differentiating, forming disorganized and heterogenous gatherings of cells in culture, and forming teratomas (tumors) in animals, in significant contrast, Applicants postnatal cells clearly do not form disorganized and heterogeneous gatherings of cells in culture and also do not form teratomas (tumors) in an animal. There is absolutely NO notation or indication in the instant application of these characteristics in the present application. Applicants submit that one of skill in the art will immediately recognize and acknowledge the significance and distinction of the postnatal nature of the claimed stem cells. This is a scientifically recognized and relevant distinction and should be taken as unanticipated and patentably distinct. One of skill in the art would readily acknowledge that the postnatal stem cells are absolutely distinct from prior described and taught embryonic stem cells or embryonic germ cells.

In particular, the skilled artisan would note, on reading and reviewing the culture studies and animal in vivo experiments described in the specification, that the postnatal animal stem cells are absolutely distinct and not anticipated by embryonic stem cells, including those of Capecchi et al. The postnatal cells described in the specification simply do not act per se like embryonic stem cells, simultaneously establishing their difference and relative usefulness versus previously described embryonic stem or germ cells. For example, the postnatal stem cells incorporate into a gel foam and retain pluripotency when the postnatal rat stem cells are administered in vivo in outbred rats, as described in the specification in Example 12 and at page 240 line 24 through page 241 line 2:

Experimental gel-foam (containing genomically-labeled stem cells) and control gel-foam (buffer only) were then randomly implanted into the right and left regions of the neck (between parotid gland and sternocleidomastoid muscle) of adult male out-bred Sprague-Dawley rats. Rats were then harvested 24 hrs after initial implantation and then at weekly intervals for five weeks thereafter. The animals were necropsied to ascertain for gross inflammatory response and the gel-foam implants removed with adherent tissues, cut into thirds and processed for histology (2 thirds)

and cell culture (1 third). Necropsy results noted no gross inflammatory response in any animal examined. Histology results noted no large infiltration of inflammatory cells into either control or experimental gel-foam pieces. Tissue culture results noted ingrowth of pluripotent stem cells into the control gel-foam and retention of pluripotency by implanted Lac-Z-labeled stem cells in the experimental gel-foam throughout the entire length of the study.

In another similar animal study, the specification at page 255 lines 5-15, describes the administration of postnatal stem cell to rats in vivo and the incorporation of the labeled cells at the site of administration and even in the bone marrow:

A2B2 B-gal PPSCs were administered and tested in vivo in an hindlimb ischemic model in rat SCID animals. The femoral artery was tied off to generate the ischemia model. PPSC cells were administered by intravenous (IV) in the rat tail vein or intramuscular (IM) locally to hindlimb prior to or after the hindlimb ischemia was generated. Histology was performed 1 week post injection of PPSCs to assess the presence and nature of B-gal labeled cells. PPSCs (B-gal positive cells) were incorporated into the hindlimb at the ischemic site when administered IM or IV. On gross anatomy review these cells appeared to track to the vasculature in the hindlimb, showing a parrallel line pattern of B-gal expression. In addition, on IV injection into an ischemic animal, significant incorporation of B-gal positive cells was observed in the bone marrow (FIGURE 44).

One skilled in the art would readily recognize and acknowledge that the described and claimed postnatal animal stem cells are absolutely, and importantly, distinct from previously described embryonic stem cells, including those used by Capecchi, and are not taught, suggested or anticipated by previously described embryonic stem cells, including those used by Capecchi.

Applicants note that claims 39, 44, 46, 47 and 50 are clear of this rejection. Applicants now present new claims 52 and 53, and submit that new claims 52 and 53 are similarly clear of this rejection. Applicants submit that claims 37, 38, 40-43, 45, 48, 49 and 51 are not anticipated by Capecchi et al. Capecchi et al does not teach or suggest the instantly claimed postnatal animal stem cells.

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's 102(b) rejection over Capecchi et al is obviated and may properly be withdrawn.

Rejection over Piedrahita et al

Claims 37, 40-43, 45, 48, 49 and 51 are rejected under 35 U.S.C. 102(b) as anticipated by Piedrahita et al [Biol of Reprod 58:1321-1329 (1998)], which teaches the generation of transgenic porcine chimeras using primordial germ cells (PGCs)-derived colonies. The Examiner asserts that Piedrahita et al anticipates the claimed invention because the PGCs they teach are capable of differentiation into the three germ layers.

Applicants respectfully disagree and traverse this rejection. To anticipate a claim, a prior art reference must teach or suggest each and every element and limitation of the claim. Claims 37, 40-43, 45, 48, 49 and 51, including as above amended, are not taught by Piedrahita et al. Applicants underscore that the instant claimed cells are isolated postnatal animal stem cells capable of self-renewal and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages, genetically engineered to express a gene or protein of interest. The claimed cells are derived from postnatal animal cells or tissues, in other words, after birth. The instantly described and claimed cells are not derived from embryonic tissue. In sharp and distinct contrast, the cells of Piedrahita are primordial germ cell derived, and were isolated from embryonic tissue, from fetuses, as described in the Abstract:

> *Primordial germ cells (PGCs) were isolated from Day 25-27 fetuses and plated on STO feeder cells in Dulbecco's modified Eagle's medium...*

Thus, the Piedrahita cells are similar to ES cells as noted at page 1321:

> *These cells, referred to as embryonic germ (EG) cells or primordial germ cell (PGC)-derived cells [16,17], are similar to ES cells with respect to markers of the undifferentiated state and their ability to colonize the germ line following injection into a host blastocyst; however, they differ in the extent of methylation of specific genes [16].*

The postnatal cells of Applicants are simply not anticipated by the prior art ES or EG or PGC cells. There is nothing in the teaching of Piedrahita that anticipates postnatal animal stem cells capable of self-renewal and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages. The instantly claimed postnatal cells are derived from postnatal cells or tissues, and are not from embryonic tissue, as noted in the specification at page 165 lines 29-32:

> *The above results demonstrate the presence and isolation of pluripotent embryonic-like stem cells, capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages from postnatal animal sources (i.e. not from embryonic tissue), particularly for humans.*

Further specification description establishes these postnatal cells in other animals, including rats, rabbits, mice, birds, including as detailed at page 225, lines 16-19 as follows:

> *This study suggests the retention of embryonic-like reserve stem cells within postnatal mammals and their potential involvement in the normal maintenance, repair and regeneration of body tissues.*

These cells are contrasted in this example in the specification (Example 11) with embryonic stem cells, at page 225 line 22 through page 226 line 3:

> *Embryonic stem cells have been identified in the blastocyst, inner cell mass and gonadal ridges of rodents and primates, including humans (Evans et al., 1981; Martin, 1981; Thomson et al., 1995, 1998; Shamblott et al., 1998; Gearhart et al, 1999). After isolation these undifferentiated cells express immunological markers for embryonic stem cell antigens, positive alkaline phosphatase staining, capabilities for extended self-renewal, and telomerase activity. When allowed to differentiate in vitro these cells express immunological markers for tissues of ectodermal, mesodermal, and endodermal origin (Thomson et al., 1995, 1998; Shamblott et al., 1998; Gearhart et al, 1999). However, when implanted in vivo the embryonic stem cells form spontaneous teratomas (Thomson et al., 1998; Gearhart et al., 1999). Because of these unique qualities embryonic stem cells have been proposed as a source of donor cells for tissue transplantations (Thomson et al., 1995, 1998; Shamblott et al., 1998; Gearhart et al, 1999).*

The current clonogenic study was undertaken to determine whether clonal populations of pluripotent stem cells were present in the connective tissues of postnatal mammals and to examine their functional capabilities.

The Piedrahita cells are derived from a porcine fetus (embryo) and have embryonic nature and character. In sharp and significant contrast, the instant claimed cells are isolated postnatal animal stem cells, capable of self-renewal and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages, genetically engineered to express a gene or protein of interest. The claimed cells are derived from postnatal animal cells or tissues, in other words, after birth. The instantly described and claimed cells are not derived from embryonic cells or tissue. The Piedrahita porcine PGCs are utilized in the generation of transgenic porcine chimeras. This could not be accomplished as described with the postnatal animal stem cells of the present invention. The instantly described and claimed cells are postnatal cells and are not derived from embryonic tissue.

As argued above with regard to Capecchi et al, Applicants submit that there exists a well recognized dogma of difference between an embryonic cell or tissue and a postnatal cell or tissue. While embryonic stem and germ cells, ES cells and the correspondingly similar EG cells, as above noted, are recognized as spontaneously differentiating, forming disorganized and heterogenous gatherings of cells in culture, and forming teratomas (tumors) in animals, in significant contrast, Applicants postnatal cells clearly do not form disorganized and heterogeneous gatherings of cells in culture and also do not form teratomas (tumors) in an animal. There is absolutely NO notation or indication in the instant application of these characteristics in the present application. Applicants submit that one of skill in the art will immediately recognize and acknowledge the significance and distinction of the postnatal nature of the claimed stem cells. This is a scientifically recognized and relevant distinction and should be taken as unanticipated and patentably distinct. One of skill in the art would readily acknowledge that the postnatal stem cells are absolutely distinct from prior described and taught embryonic stem cells or embryonic germ cells.

In particular, the skilled artisan would note, on reading and reviewing the culture studies and animal in vivo experiments described in the specification, that the postnatal animal stem

cells are absolutely distinct and not anticipated by embryonic stem cells, including those of Piedrahita et al. The postnatal cells described in the specification simply do not act per se like embryonic stem cells, simultaneously establishing their difference and relative usefulness versus previously described embryonic stem or germ cells. For example, the postnatal stem cells incorporate into a gel foam and retain pluripotency when the postnatal rat stem cells are administered in vivo in outbred rats, as described in the specification in Example 12 and at page 240, as quoted above with regard to the Capecchi et al reference arguments. In another similar animal study, the specification at page 255 lines 5-15, describes the administration of postnatal stem cell to rats in vivo and the incorporation of the labeled cells at the site of administration and even in the bone marrow, again as quoted above with regard to the Capecchi et al reference arguments. One skilled in the art would readily recognize and acknowledge that the described and claimed postnatal animal stem cells are absolutely, and importantly, distinct from previously described embryonic stem cells, embryonic germ cells, or primordial germ cells, including those used by Piedrahita, and are not taught, suggested or anticipated by previously described embryonic stem cells, embryonic germ cells, or primordial germ cells, including those used by Piedrahita.

Applicants note that claims 38, 39, 44, 46, 47 and 50 are clear of this rejection. Applicants now present new claims 52 and 53, and submit that new claims 52 and 53 are similarly clear of this rejection. Applicants submit that claims 37, 40-43, 45, 48, 49 and 51 are not anticipated by Piedrahita et al. Piedrahita et al does not teach or suggest the instantly claimed postnatal animal stem cells.

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's 102(b) rejection over Piedrahita et al is obviated and may properly be withdrawn.

The §103 Rejection

Claims 37-45 and 47-51 are rejected under 35 U.S.C. 103(a) as unpatentable over Shamblott [PNAS 95:13726-13731 (1998)] when taken with Sambrook et al [Molecular Cloning, Book 3, 1989]. The Examiner has previously cited Shamblott et al. as teaching the generation of human pluripotent stem cells from gonadal ridges and mesenteries containing primordial germ cells (PGCs) and teaching that embryoid bodies collected from these cultures revealed a wide variety of differentiated cell types, including derivatives of all three embryonic germ layers. The Examiner asserts that the claims do not distinguish between the cells of Shamblott and the cells that are instantly claimed. The rejected claims are alleged to not provide any requisite characteristics that differentiate the claimed stem cells from, for example, the PGCs taught by Shamblott. The Examiner remarks in particular that Shablott et al teach that gonadal ridges and mesenteries of 5 to 9 week old human fetuses and cells initially cultured on a layer of mouse STO fibroblast feeder layer formed embryoid bodies that demonstrated derivatives of the three embryonic germ layers. The Examiner further states that "the claims recite that the embryonic-like stem cells are 'derived from non-embryonic or postnatal antmal cells or tissue', however this recitation does not differentiate them from the cells as taught by Shamblott". While Shamblott does not teach transfection of the stem cells to produce a genetically engineered cell, Sambrook is applied and combined as teaching methods of tranfecting mammalian cells with any gene of interest.

Applicants respectfully disagree with the Examiner and traverse this rejection, asserting that the claimed stem cells are distinguished from the Shamblott PGC cells and are not rendered obvious by the combination of the Shamblott and Sambrook references. To establish a prima facie case of obviousness, the prior art reference(s) must, alone or in combination, teach or suggest all the claim limitations. Shamblott's PGCs are absolutely distinct and do not anticipate, or make obvious, Applicant's postnatal stem cells. The addition of or combination of Sambrook to Shamblott's cells does not serve to make Applicant's cells or method of isolating them obvious from Shamblott's cells. Applicants underscore that the instant claimed cells are <u>isolated postnatal animal stem cells</u> capable of self-renewal and capable of differentiation to cells of

endodermal, ectodermal and mesodermal lineages, genetically engineered to express a gene or protein of interest. The claimed cells are derived from postnatal animal cells or tissues, in other words, after birth. The instantly described and claimed cells are not derived from embryonic tissue. In sharp and distinct contrast, the cells Shamblott of are primordial germ cell derived, and were isolated from embryonic tissue, from fetuses, as described above and argued with regard to Piedrahita, and similarly argued with regard to the embryonic stem cells of Capecchi.

The Shamblott cells are derived from a human fetuses (5-9 weeks postfertilization) and have embryonic nature and character. In sharp and significant contrast, the instant claimed cells are isolated postnatal animal stem cells, capable of self-renewal and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages, genetically engineered to express a gene or protein of interest. The Shamblott human PGCs form embryoid bodies (EB) in culture and difficulties with complete cell disaggregation are noted (see page 13729 and 13730). In contrast, the postnatal animal stem cells of the present invention do not demonstrate these qualities or characters.

As argued above with regard to Capecchi et al and Piedrahita et al, Applicants submit that there exists a well recognized dogma of difference between an embryonic cell or tissue and a postnatal cell or tissue. While embryonic stem and germ cells, ES cells and the correspondingly similar EG cells, as above noted, are recognized as spontaneously differentiating, forming disorganized and heterogenous gatherings of cells in culture, and forming teratomas (tumors) in animals, in significant contrast, Applicants postnatal cells clearly do not form disorganized and heterogeneous gatherings (or aggregates) of cells in culture and also do not form teratomas (tumors) in an animal. There is absolutely NO notation or indication in the instant application of these characteristics in the present application. Applicants submit that one of skill in the art will immediately recognize and acknowledge the significance and distinction of the postnatal nature of the claimed stem cells, particularly and importantly as compared to an embryonic human cell. This is a scientifically recognized and relevant distinction and should be taken as unanticipated and patentably distinct. One of skill in the art would readily acknowledge that the postnatal stem cells are absolutely distinct from prior described and taught embryonic stem cells or embryonic

germ cells.

In particular, the skilled artisan would note, on reading and reviewing the culture studies and animal in vivo experiments described in the specification, that the postnatal animal stem cells are absolutely distinct and not anticipated or suggested by embryonic stem cells, including those of Shamblott et al. The postnatal cells described in the specification simply do not act per se like embryonic stem cells, simultaneously establishing their difference and relative usefulness versus previously described embryonic stem or germ cells, particularly including human embryonic stem cells. For example, the postnatal stem cells incorporate into a gel foam and retain pluripotency when the postnatal rat stem cells are administered in vivo in outbred rats, as described in the specification in Example 12 and at page 240, as quoted above with regard to the Capecchi et al reference arguments. In another similar animal study, the specification at page 255 lines 5-15, describes the administration of postnatal stem cell to rats in vivo and the incorporation of the labeled cells at the site of administration and even in the bone marrow, again as quoted above with regard to the Capecchi et al reference arguments.

One skilled in the art would readily recognize and acknowledge that the described and claimed postnatal animal stem cells are absolutely, and importantly, distinct from and non-obvious over previously described embryonic stem cells, embryonic germ cells, or primordial germ cells, including those used by Shamblott, and are not taught, suggested or anticipated by previously described embryonic stem cells, embryonic germ cells, or primordial germ cells, including those used by Shamblott. The addition of Sambrook adds nothing relevant to the particularity of the cells of Shamblott, and simply establishes teaching as to genetically manipulating cells.

Applicants note that claim 46 is clear of this rejection. Applicants now present new claims 52 and 53, and submit that new claims 52 and 53 are similarly clear of this rejection. Applicants submit that claims 37-45 and 47-51 are not suggested or deemed obvious by Shamblott et al, alone or when taken with Sambrook et al. Shamblott et al, alone or when taken with Sambrook et al, does not teach or suggest the instantly claimed postnatal animal stem cells.

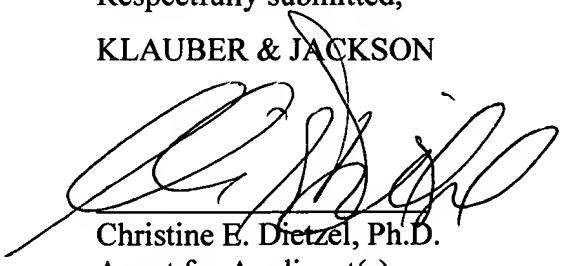
In view of the foregoing amendments and remarks, Applicants submit that the Examiner's 103 rejection is obviated and may properly be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Should the Examiner feel that further issues remain upon a review of this Response, she is invited to call the undersigned at the number listed below to effect their resolution. Early and favorable action on the claims is earnestly solicited.

No additional fees are believed to be necessitated by this response, however, in the event the U.S. Patent and Trademark office determines that claim fees, a further extension and/or other relief is required, applicant petitions for any required relief including extensions of time and claim fees and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 11-1053** referencing Docket No. 1304-1-019CIP.

Respectfully submitted,
KLAUBER & JACKSON



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